Improving patient outcomes in colorectal cancer surgery

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CHAPTER 1

Introduction and outline of this thesis

INTRODUCTION

Colorectal cancer afflicts approximately 1,361,000 patients every year and accounts for 694,000 deaths per year worldwide. In females it is the second most common form of cancer, after breast cancer, and in males it is the third most common form after prostate and lung cancer.[1,2]

At the start of the twentieth century, colorectal cancer was an incurable disease. Especially rectal cancer had mortality rates of 100% and recurrence at the surgical site (local recurrence) in 80% of patients.[3]

In the 20th century however, great improvements were made. It started in 1908 when Miles published the concept of cylindrical lymphatic spread of cancer cells and the recommendation to perform more extensive surgical resection including the lymph nodes, in order to prevent recurrence. This procedure was called 'abdominoperineal resection' (APR) and is considered the basis for modern rectal cancer surgery.[4] Although clear improvements in survival and recurrence rates were seen, prognosis was still poor with local recurrence rates of up to 40% and 5-year survival rates below 50%. [5] This didn't improve until Heald introduced the concept of 'total mesorectal excision' (TME) in 1982, in which sharp dissection of the rectum and the surrounding fatty envelop with the lymph nodes and radially spreading tumor cells (mesorectum) is performed. This revolutionized rectal cancer surgery with local recurrence rates in a selected patient group of around 3.7% and 5-year survival rates of up to 87% after surgery.[6,7] For the overall rectal cancer population however, there was still a significant problem withlocoregional recurrence despite the advancements made by TME surgery.

The addition of preoperative radiotherapy to TME surgery was shortly hereafter introduced with great effect. The rate of local recurrence at two years in the Dutch TME trial was 2.4 percent in the radiotherapy-plus-surgery group and 8.2 percent in the surgery-only group ($P<0.001$).[8]

Today TME surgery is still the gold standard for rectal cancer surgery and combined with (chemo) radiotherapy this is the most potent curative treatment for patients with rectal cancer.

In the early 1990's laparoscopic (minimally invasive) surgery was introduced. Instead of operating through one large abdominal incision, several small incisions are made and surgery is performed with smaller instruments and a laparoscope, producing a magnified image of the operating field. The introduction of minimally invasive surgery has resulted in less perioperative blood loss, faster postoperative recovery, less pain and a shorter length of hospital stay while reporting similar radicality and specimen margins as well as recurrence and survival rates for colon cancer in several large trials.[9–11] Subsequently, laparoscopic surgery was introduced for patients with rectal cancer. Mainly because

of the limited workspace in the lower pelvis and fibrosis due to neoadjuvant therapy, rectal cancer surgery is considered more challenging than colon surgery. Nonetheless, laparoscopic surgery did result in short term benefits for patients with rectal cancer as shown in **chapter 2** of this thesis. There were remaining questions however whether laparoscopic surgery for rectal cancer surgery was non-inferior to open surgery in terms of survival and locoregional recurrence rates, since evidence was lacking from large randomized trials. To conclusively answer this question the COLOR II trial was initiated with randomization of over 1000 patients between open and laparoscopic surgery.[12] The results of oncological outcome in the COLOR II trial are described in **chapter 3**. Besides oncological outcome, other patient centered outcomes are important as well. A number of consequences affecting the patients' quality of life have been observed after completed treatment for rectal cancer, including sexual dysfunction and urinary incontinence. [13,14] Nerve pathways as well as microvasculature are easily injured during rectal cancer surgery as a result of dissection during TME and due to radiotherapy among other factors. The incidence of sexual and urinary complications after open rectal surgery is in the range of 10-35% and < 5%, respectively. [15,16] Sexual and urinary function after laparoscopic TME were not reported before in prospective randomized trials, but it was incorporated in the COLOR II and described in **chapter 4** of this thesis.

Furthermore, one of the major clinical problems in the postoperative phase after both colon and rectal cancer surgery are infectious complications with an incidence of 20-40%.[9,17,18] Anastomotic leakage is the most severe complication of colorectal surgery with an incidence ranging from 4% to 28% depending on definitions, but generally considered to average 5-15%.[2,19] Multiple variables have been posed as possible risk factors including impaired vascularization of the anastomosis, mechanical traction, and the patient's own microbiome.[20]

The additional morbidity as well as mortality associated with anastomotic leakage is substantial with reported rates ranging from 2% to 30%.[21,22] Treatment of complications after colorectal cancer surgery requires specialized care and is associated with major health-care costs.

Endogenous bacteria residing in the digestive tract cause the vast majority of surgical site infections following colorectal surgery.[23,24] By definition, the integrity of this mucosal barrier is affected by colorectal surgery. Moreover, the composition of intestinal flora shows profound changes following colorectal surgery, which may be influenced by delayed or impaired gut peristalsis in the postoperative phase.[25,26] The introduction of prophylactic antibiotics in patients undergoing colorectal surgery has reduced the risk of general infectious complications by approximately 70 % although its prevalence is still quite high around 20-40%.[27]

Selective decontamination of the digestive tract (SDD) is a way to reduce aerobic Gram-negative bacterial load. SDD is based on the administration of oral nonabsorbable antibiotics and designed as an antimicrobial prophylaxis regime to prevent or minimize the impact of endogenous infections by potentially pathological microorganisms.[28,29] Its use and possible benefits in digestive surgery are discussed in **chapter 6**.

This prompted us to further investigate SDD in a randomized controlled trial: Perioperative Selective Decontamination of the Digestive Tract (SDD) in Elective Colorectal Cancer Patients: a Multicenter Randomized Clinical Trial (SELECT), which is described in **chapter 7.** Primary outcome of this multicenter randomized controlled trial was anastomotic leakage rates and infectious complications after surgery, which are addressed in **chapter 8.**

In recent years polymerase chain reaction (PCR) based profiling techniques have been developed to get a clearer understanding of the exact composition of the microbiome and its changes under pathological circumstances. Until now all information about the microbiome was culture based, leaving the majority of the microorganisms undetected. PCR-based profiling techniques for high throughput analysis of the human intestinal microbiota provide insight on a much more detailed level than conventional culture based techniques.[30] To ensure adequate decontamination and to study the effects of colorectal cancer and SDD in the patients of the SELECT Trial, a PCR based analysis technique called IS-pro was used and microbiome data was acquired. **Chapter 9** further elaborates on the effects of SDD on the microbiome.

Finally the results of the studies described in this thesis are summarized and future developments and implementation of the SDD regimen are discussed in **chapter 10.**

The research questions addressed in this thesis are:

1. Is laparoscopic rectal cancer surgery non-inferior to open surgery on short term outcome and local recurrence rates?
2. What are the effects of laparoscopic and open surgery for rectal cancer on sexual function and urinary incontinence?
3. Can postoperative infectious complications and anastomotic leakage be diminished with perioperative SDD?
4. What are the effects of SDD on the patients' microbiome?

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